REMARKS

Upon entry of the foregoing amendment, claims 29, 30, 35 and 44-62 will be pending. Claims 1-28, 32-34, and 36-43 were previously cancelled without prejudice to, or disclaimer of, the underlying subject matter in Applicants' Response dated November 21, 2007. Claim 31 is hereby cancelled without prejudice or disclaimer. Claims 30, 57, and 62 were withdrawn by the Examiner as being drawn to non-elected subject matter. Office Action at page 2. By way of the present amendment, claims 29, 30, 50, 51, 56, 57, 59, and 60 have been amended without prejudice or disclaimer solely to clarify the claimed subject matter. For example, consistent with current case law, the singular "a" in amended claims 30, 57, and 60 should be read as "one or more." Support for the amended claims and new claim can be found in the claims as originally filed, and in the specification at page 5, lines 9-17. No new matter enters by way of this amendment.

I. Election/Restriction

Applicants acknowledge the finality of the restriction requirement. Applicants respectfully disagree with and traverse the Examiner's withdrawal of claims 30, 57, and 62 as being drawn to non-elected inventions. At the outset, Applicants believe that claims 30, 57, and 62 are not drawn to non-elected inventions, and invite the Examiner to state the group in the Restriction Requirement mailed September 21, 2007 in which claims 30, 57 and 62 should be placed. Furthermore, claims 30, 57, and 62 provide limitations that further define the genetic construct recited in elected claim 29, and hence should not be withdrawn as being drawn to a non-elected invention.

Applicants understand that the claims drawn to non-elected inventions may be prosecuted in divisional applications. Applicants further understand claims 29, 35, 47, 51, 53, and 56 are considered generic with respect to all species elections made in Applicants' Response dated November 21, 2007 and are under consideration to the extent that they read on the elected species. Applicants reserve the right to consideration of additional species upon the finding of an allowable generic claim.

II. Information Disclosure Statement

Applicants thank the Examiner for the Examiner-initialed copy of the PTO/SB/8a and PTO-1449 forms, indicating Examiner's consideration of information disclosure statements submitted by Applicants on September 14, 2006 and March 23, 2007.

III. Objections to the Specification and Abstract

The specification has been objected to for failure to comply with the text and formatting requirements of 37 C.F.R. § 1.52(b)(2). Office Action at page 3. In order to facilitate prosecution, Applicants submit herewith a substitute specification and a request for its entry as a separate paper accompanying this Response.

The attached substitute specification has been amended to contain text written in Time New Roman font and lines that are 1.5 spaced to comply with the formatting and spacing requirements of 37 C.F.R. § 1.52 (b)(2). The attached substitute specification has also been amended to contain page numbers centrally below the text to comply with the page-numbering requirement of 37 C.F.R. § 1.52 (b)(5).

The abstract has been objected to because it does not commence on a separate sheet in accordance with 37 C.F.R. § 1.52(b)(4). Office Action at page 3. The attached substitute specification has been amended to contain an abstract commencing on a separate sheet to render the rejection under 37 C.F.R. § 1.52(b)(4) moot.

The specification has also been objected to under 37 C.F.R. § 1.57(d) because it contains an embedded hyperlink and/or other form or browser-executable code. Office Action at page 3. The hyperlink found on page 13, line 2 of the originally filed specification has been removed in order to render the rejection under 37 C.F.R. § 1.57(d) moot.

Finally, the Examiner states that neither the sequences depicted in Figure 3, nor the description of the drawing, refer to the sequences by SEQ ID NO. as required by 37 C.F.R. §§ 1.821 - 1.825. Office Action at page 4. Applicants have included SEQ ID NO's to refer to nucleic acid sequences in the paragraph on page 6, line 29 to page 7, line 3 in the Substitute Specification submitted herewith in order to comply with 37 C.F.R. §§ 1.821-1.825. Applicants have also included SEQ ID NO's for nucleic acid sequences contained in the paragraph

beginning on page 15, line 8 of the Substitute Specification submitted herewith in order to comply with 37 C.F.R. §§ 1.821-1.825.

As such, Applicants respectfully request that these objections are moot and that they be withdrawn.

IV. Failure to Comply with Nucleotide and/or Amino Acid Sequence Disclosures (37 C.F.R. § 1.821 - 1.825

The Examiner alleges that neither the sequences depicted in Figure 3, nor the description of Figure 3 in the specification, contain necessary references to SEQ ID NO's. Office Action at page 4. In order to facilitate prosecution, Applicants have included SEQ ID NO's to refer to nucleic acid sequences in the brief description (the paragraph on page 6, line 29 to page 7, line 3) of Figure 3 in the Substitute Specification submitted herewith. Applicants have also included SEQ ID NO's to refer to nucleic acid sequences contained in the paragraph beginning on page 15, line 8 of the Substitute Specification submitted herewith. In addition, Applicants have submitted herewith a paper copy and computer-readable form (CRF) of a Sequence Listing containing the appropriate sequences disclosed in the specification (SEQ ID NO's 1-16).

The Examiner further alleges that "the brief description of Figure 3 additionally contains short amino acid motifs, absent corresponding SEQ ID NOS." Office Action at page 4. Applicants respectfully assert, however, that the motif sequences contained in the brief description of Figure 3 ("RGYW" and "WRCY") are DNA sequences and therefore do not meet the requirements for inclusion in the Sequence Listing.

As such, Applicants respectfully request that Applicants' alleged failure to comply with nucleotide and/or amino acid sequence disclosures under 37 C.F.R. § 1.821 - 1.825 is moot and should be withdrawn.

V. Claim Rejections under 35 U.S.C. § 102

Claims 29, 35, 44-56, and 58-61 stand rejected under 35 U.S.C. § 102(e) as being anticipated by Sale *et al.*, U.S. Patent Application Publication No. 2005/0026246 ("the '246 publication"). Office Action at page 4. Applicants disagree with the Examiner's rejection and request withdrawal for the following reasons.

It is well established that to anticipate a claim, a reference must disclose every element of the claim. *Verdegaal Bros. v. Union Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). The Examiner has done nothing more than locate in the '246 publication terms from the claims. While common terms may exist in the two applications, the claimed subject matter is distinct.

At the outset, the '246 publication does not disclose every element of claim 29. According to the '246 publication, example 8 of the '246 publication suggests the deletion of a RAD51 paralogue (XRCC2 or XRCC3) in a wild-type DT40 cell. The resulting cell allegedly gains the ability to diversify the endogenous immunoglobulin locus by hypermutation. *See* paragraphs [0182] and [0195] of the '246 publication. The '246 publication further suggests that only after the deletion of a RAD51 paralogue can the DT40 cell be used in a method for diversifying a transgene. *See* paragraph [0032] and claim 23 of the '246 publication. At the same time, however, the '246 publication asserts that cell mutants having deficiency in XRCC2 or XRCC3 exhibit chromosomal instability which can be responsible for at least some of the observed diversification events. *See* paragraph [0183] of the '246 publication. According to the '246 publication, this instability makes the DT40 cells deficient in XRCC2 or XRCC3 unsuitable for use in a method for selective genetic diversification. *See* paragraph [0183] of the '246 publication. As such, because RAD51 is apparently an essential gene for homologous recombination (including gene conversion), the '246 publication suggests that it would be practically impossible to integrate a target gene (transgene) at a defined location such as the immunoglobulin locus and to maintain the stability and vitality of RAD51-negative cells for a prolonged period of time.

According to the '246 publication as recited above, the method of instant claim 29 would not function with a RAD51-negative DT40 cell, since transfection of a RAD51 negative cell with a transgene would not be practicable for producing a lymphoid cell capable of selective genetic diversification by hypermutation. In contrast, the lymphoid cell recited in the method of claim 29 contains no deleterious mutations in genes encoding paralogues and analogues of the RAD51 protein and hence allows efficient integration of transfected constructs and their diversification for essentially unlimited period of time. In summary, the lymphoid cell, or "starting material"

for transfection, as recited in the method of claim 29, is different from the genetically engineered DT40 cell referred to in the '246 publication.

In support of the anticipation rejection, the Examiner alleges that the '246 publication teaches "a method for generating diversity by preparing an antibody-producing cell line capable of directed constitutive hypermutation of a specific nucleic acid region, comprising selecting a cell in which the rate of V gene mutation exceeds that of other gene mutation." Office Action at page 5. As support, the Examiner points to the title and abstract. Yet, neither the title "Method for Generating Diversity" nor the slightly longer abstract recite Applicant's claims. For example, the allegedly taught method of the '246 publication abstract does not suggest "transfecting a lymphoid cell capable of gene conversion" or "wherein said lymphoid cell comprising said target nucleic acid sequence contains no deleterious mutations in genes encoding paralogues and analogues of the RAD51 protein."

The Examiner further states that "[a] cell capable of directed constitutive hypermutation is taught by [the '246 publication] as a genetically manipulated chicken DT40 cell" and then points to Applicant's claims and, presumably, claim 30 in the '246 publication.[1] Office Action at page 5. But claims do not teach, specifications do. *See* SRI Int'l v. Matsushita Elec. Corp., 775 F.2d 1107, 1121, 227 U.S.P.Q. 577, 585 (Fed. Cir. 1985). Moreover, claim 30 is a composition claim and Applicant's claims are method claims. In addition, the claim limitations such as "wherein said lymphoid cell contains no deleterious mutations in genes encoding paralogues and analogues of a RAD51 protein" are not present anywhere on the cited page. In fact, the opposite is true; the cells claimed in the '256 publication have deletions in genes encoding paralogues and analogues of a RAD51 protein (Δ xrcc2 DT40 and Δ xrcc3 DT40). *See* claim 31 of the '246 publication on page 48.

The Examiner has simply found claim terms out of context in the '246 publication and repeated them in the Office Action. Office Action at pages 5-6.

> It is therefore evident from the foregoing that a parental chicken bursal lymphoma DT40 cell line is capable of gene conversion (a further limitation of claim 29) and contains the RAD54 gene, without any deleterious mutations in genes encoding paralogues

[1] Applicants note that U.S. Patent No. 7,368,259, which issued from U.S. Patent Application No. 10/733,532 (published as the '246 publication), did not contain claim 30.

> and analogues of the RAD51 protein (a yet further limitation of claim 29).

Id. This is not a showing of anticipation. The Examiner has not demonstrated that the parental chicken bursal lymphoma DT40 cell line described above is capable of selective genetic diversification of a transgenic target nucleic acid sequence by hypermutation as recited in Applicant's claims. The Examiner points to nowhere in the '246 publication that teaches or suggests that cells having no deleterious mutations in genes encoding paralogues or analogues of a RAD51 protein are capable of hypermutation. *See instead* paragraphs [0025], [0037], [0094] to [0098], [0193], and Examples 8 and 9 of the '246 publication. Even if the '246 publication teaches that cells which lack one or more copies of a RAD51 paralogue become capable of hypermutation, the claimed methods are not anticipated since the recited lymphoid cells contain no deleterious mutations in genes encoding paralogues and analogues (XRCC2, XRCC3) of the RAD51 protein. *See* Claim 29.

The Examiner has also located terms from the dependent claims in the '246 specification, but these still do not teach the claimed invention. The Examiner alleges that paragraph [0181] of the '246 publication teaches that "compared to the parental DT40 line, a mutant that lacks RAD54 shows a considerably diminished proportion of sIgM-loss variants," indicating a loss of gene conversion activity. Office Action at pages 5-6. The Examiner then claims that "[i]t is therefore evident from the foregoing that a parental chicken bursal lymphoma DT40 cell line is capable of gene conversion...and contains the RAD54 gene, without any deleterious mutations in genes encoding paralogues and analogues of the RAD51 protein..." The Examiner does not even allege, let alone show, that DT40 cells comprising RAD54 having no deleterious mutations in genes encoding paralogues and analogues of RAD51 gain the capability of selective genetic diversification by hypermutation, as is recited in instant claim 29.

In summary, whatever the '246 publication teaches or suggests, it does not teach or suggest a method for producing a cell capable of selective genetic diversification of a transgenic target nucleic acid sequence by hypermutation including transfecting a lymphoid cell capable of gene conversion with a genetic construct containing the target nucleic acid sequence into the immunoglobulin locus of the lymphoid cell, where the lymphoid cell transfected with the construct contains no deleterious mutations in genes encoding paralogues and analogues of the

RAD51 protein and is capable of hypermutation. In fact, the Applicants discuss the work by Sale and coauthors in the instant specification. *See* Specification at page 3, lines 5-27 and page 9, lines 26-29 ("It was previously reported that the deletion of RAD51 paralogues induces Ig hypermutation in DT40 (Sale et al., 2001)"; "...disruptions of the RAD51 paralogues not only decrease Ig gene conversion, but also induce Ig hypermutation (Sale et al., 2001)..."). For the foregoing reasons, Applicants respectfully request withdrawal of the rejections of claims 29, 35, 44-56, and 58-61 under 35 U.S.C. § 102(e).

VI. Claim Rejections under 35 U.S.C. § 103

Claims 29 and 31 stand rejected under 35 U.S.C. § 103 as being anticipated by Sale *et al.* (U.S. Patent Application Publication No. 2005/0026246) in view of Grawunder *et al.* (U.S. Patent Application Publication No. 2006/0052585). Office Action at page 7. Applicants respectfully disagree with the Examiner's rejection and request withdrawal for the following reasons. This obviousness rejection in view of the '246 publication has been overcome by the arguments set forth above with respect to 35 U.S.C. § 102. As Applicants have set forth above, the '246 publication does not show that a parental chicken bursal lymphoma DT40 cell line without any deleterious mutations in genes encoding paralogues and analogues of the RAD51 protein, is capable of hypermutation. Nothing in Grawunder *et al.* makes up the above-mentioned deficiency of Sale *et al.*

The Supreme Court recently addressed the issue of obviousness in *KSR International Co. v. Teleflex Inc.*[2] In *KSR* the Court stated that the *Graham v. John Deere Co*,[3] factors still control an obviousness inquiry. Those factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness.[4] The Court also stated that, where there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. *KSR International Co.*, 127 S. Ct. at 1742. It is recognized that the "gap between the prior art and the claimed invention may not be

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[2] 127 S. Ct. 1727 (2007).
[3] 383 U.S. 1 (1966).
[4] *KSR*127 S. Ct. at 1734 (quoting *Graham*, 383 U.S. at 17-18).

'so great as to render the [claimed invention] non-obvious to one reasonably skilled in the art.'"[5] Moreover, Patent Office personnel must provide an explanation to support an obviousness rejection. *Id.* at 57,527. That explanation must include a rational underpinning to support the legal conclusion of obviousness, which cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning.[6]

Applicants respectfully assert that the Office has failed to establish a *prima facie* case of obviousness because, even when combined, the teachings of the '246 publication and Grawunder *et al.* do not teach or suggest all the instant claim limitations. Whatever else the combination of the '246 publication and Grawunder *et al.* teaches or suggests, it does not teach or suggest a method for producing a cell capable of selective genetic diversification of a transgenic target nucleic acid sequence by hypermutation comprising transfecting a lymphoid cell capable of gene conversion with a genetic construct containing said target nucleic acid sequence into the immunoglobulin locus of said lymphoid cell, wherein said lymphoid cell comprising said target nucleic acid sequence contains no deleterious mutations in genes encoding paralogues and analogues of the RAD51 protein and is capable of hypermutation.

For the foregoing reasons, Applicants respectfully request withdrawal of the rejections of claims 29 and 31 under 35 U.S.C. § 103.

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[5] Examination Guidelines for Determining Obviousness under 35 U.S.C. § 103 in view of the Supreme Court Decision in *KSR International v. Teleflex, Inc.* Fed. Reg. 57,526, 57,528 (Oct. 10, 2007) (relying on and quoting from *Dann v. Johnson*, 425 U.S. 219, 230 (1976)).

[6] *See, KSR International Co.* 127 S. Ct. at 1741 (discussing obviousness analyses and citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

CONCLUSION

In view of the above, each of the presently pending claims is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding objections and rejections of the claims, and to pass this application to issue. The Examiner is encouraged to contact the undersigned at (202) 942-5186 should any additional information be necessary for allowance.

Respectfully submitted,

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